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Occupational physical activity and non-Hodgkin's lymphoma

[Epidemiology]

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ABSTRACT

Occupational physical activity and non-Hodgkin's lymphoma. *Med. Sci. Sports Exerc.,* Vol. 31, No. 4, pp. 566-571, 1999.

Purpose: The purpose of this study was to evaluate the role of physical activity in the development of non-Hodgkin's lymphoma (NHL).

Methods: Incident NHL cases and population-based controls were identified from three case-control studies conducted in four midwestern states: Iowa, Kansas, Minnesota, and Nebraska. A total of 1177 cases (993 men, 184 women) and 3625 controls (2918 men, 707 women) were interviewed. Usual occupation (all states) and lifetime occupational histories (Iowa and Minnesota only), obtained from interviews, were classified for energy expenditure (EE) and sitting time. Odds ratios (OR) and 95% confidence intervals were calculated comparing moderate and high activity levels with sedentary levels.

Results: There was no evidence of an association between NHL and occupational physical activity measured either by EE or sitting time. Among men, the OR associated with usual occupation moderate and high EE were 1.1 and 1.0, respectively. For sitting time, the OR were also 1.1 and 1.0 for moderate and high activity, respectively. Among women, slight nonsignificant elevations in risk of NHL were observed among the high energy level and high activity sitting categories. The trends were not significant. There was no evidence of confounding or effect modification by vital status, hair dye use, or solvent exposure. Among subjects with lifetime occupational histories, there were no significant increases or trends for cumulative or average EE or sitting time. There was no association between occupational physical activity and NHL.

Conclusion: Research on nonoccupational physical activity, which in the U.S. is likely the more

important component of daily activity than occupational activity, may still be warranted given the laboratory evidence linking physical activity and immune function, an important factor in the etiology of NHL.

The relationship between physical activity and cancer risk is of considerable public health importance (48). Evidence suggests that colon cancer risk is lower among individuals who engage in regular, moderate physical activity (28,43,50), whether physical activity is measured as lifetime occupational activity, leisure time or recreational physical activity, or as physiological fitness. Physical activity may also affect the risk of breast cancer (4,10,13-15), endometrial cancer (31,45), and prostate cancer (1,30,53), although the magnitude and direction of these associations have been inconsistent.

We (24,26,27) and others (54-56) have hypothesized that the associations between physical activity and cancer may be related to exercise-induced changes in immune function. Acute, moderate to intense exercise in humans is accompanied by a transient immunosuppression of lymphocyte functions (29), and transient immunosuppression among athletes and others engaged in heavy exercise appears to make them more susceptible to upper respiratory tract infections (34). Individuals who are immunosuppressed because of congenital or acquired immunodeficiency states (12,36) appear to be at considerably higher risk for non-Hodgkin's lymphoma (NHL). It is not known, however, whether transient and repeated exercise-induced immunosuppression increases the risk for lymphoma.

The purpose of this study was to evaluate the role of physical activity in the development of NHL using data from three case-control studies conducted in four Midwestern states.

METHODS

Subjects. Cases of NHL were ascertained from four states: Iowa, Kansas, Minnesota, and Nebraska. White men and women aged 21 yr or older from eastern Nebraska and newly diagnosed with NHL between July 1, 1983, and June 30, 1986, were identified through the University of Nebraska Medical Center Lymphoma Study Group and a special surveillance of area hospitals. White men aged 21 yr and older between 1976 and 1982 (Kansas), between March 1981 and October 1983 (Iowa), or between October 1980 and September 1982 (Minnesota) were identified through state cancer registries (Iowa and Kansas) and a special surveillance of area hospitals (Minnesota). Population-based controls without hematopoietic or lymphatic cancer were randomly selected by random digit dialing (aged < 65 yr) and by a sample of the Health Care Financing Administration files (aged 65 yr or older). Controls were frequency matched by gender, age (± 2 yr for Nebraska and Kansas; ± 5 yr for Iowa and Minnesota), state of residence, and vital status. The response rates in the cases ranged from 89-96%. The response rates in the controls, taking into account participation rates in the first household census phase of the random digit dialing procedure, ranged from 77-93%. Further details concerning subject ascertainment and the interviewing process are reported elsewhere (8,23,58).

There were 1,177 cases (993 men, 184 women) and 3,625 controls (2,918 men, 707 women)

in the combined study; the age at diagnosis was 20-44 yr (112 cases, 490 controls), 45-64 yr (383 cases, 1,028 controls), 65-74 yr (328 cases, 931 controls), 75+ yr (353 cases, 1,162 controls), unknown age (2 cases, 14 controls). The number of subjects by state of residence was 292 cases, 603 controls for Iowa; 170 cases, 948 controls for Kansas; 329 cases, 642 controls for Minnesota; and 385 cases, 1,432 controls for Nebraska.

Occupational data. The three case-control studies (four states with one of the case-control studies including two states) collected varying amounts of occupational data per subject. Complete lifetime occupational histories were available only in the Iowa/Minnesota study. Less information is available for subjects from Kansas and Nebraska. Consequently, analyses of the combined data from the three studies were based on usual occupation, which was asked directly in the Kansas study and could be derived in the other two studies.

In Iowa and Minnesota the usual occupation and industry were derived from the lifetime farming and nonfarming occupational histories by identifying the longest held job after combining the durations of jobs with the same occupational codes. For example, the duration of all mechanic jobs per subject summed to calculate total mechanic duration.

In Nebraska subjects were asked whether they had ever lived or worked on a farm and, if so, about years of pesticide use. The total years of working on a farm was not directly asked. In addition, the longest nonfarm job was asked with years started and ended. To identify usual occupation and industry for persons who ever worked or lived on a farm, the calendar year and duration of farming was estimated from the years of pesticide use and compared with age and the longest nonfarm job. If all farming experience occurred before 18 yr, nonfarm data were used as usual occupation and industry; if the farm years after 18 yr were greater than the duration of the longest nonfarm job, then farming was considered the usual occupation.

Occupational histories were determined from different item lists depending on the study. For Iowa and Minnesota, items included names and locations of employers, types of business, job title, years worked, full-time/part-time work, and activities or duties. We used the lifetime occupational history and also derived the usual (i.e., longest) job from the history after combining the duration of jobs with the same occupational codes. For Kansas, items included usual occupation, years worked, duties, kind of company, and name and location of company. For Nebraska, the longest nonfarm job was determined by asking "what did you do, what kind of company, and year started and stopped." For the farm jobs, a crude surrogate for years in a farm job was derived by looking at the years started and stopped and pesticide use. Comparing the two categories (nonfarm and farm) and checking that the year on the farm came after age 18, the longest job for the usual job was selected.

Subjects were excluded: 1) if they had never worked, 2) if it was not possible to identify the usual occupation from the work history, 3) if the usual occupation could not be classified as to physical activity, or 4) if age was unknown, yielding 985 cases and 2,871 controls in the analysis.

Occupational job titles were coded with the 1977 Standard Occupational Classification system (47) in Kansas and Nebraska and with the 1977 Dictionary of Occupational Titles (49) in Iowa and

Minnesota. Industry was not used to determine the physical activity measures other than to clarify the occupational coding.

Physical activity measures. Assessment of physical activity was based on usual occupation and included two measures: EE and sitting time. The index of EE was based on the rating system of Hettinger et al. (22) and used by Vetter et al. (50) and Dosemeci et al. (11). Sedentary activity was considered to be occupational work where EE was < 8 $kJ \cdot min^{-1}$ for men and < 5 $kJ \cdot min^{-1}$ for women. Jobs in which EE was 8-12 $kJ \cdot min^{-1}$ for men and 5-8 $kJ \cdot min^{-1}$ for women were classified as ones with moderate activity. Heavy activity was work with an estimated EE of > 12 $kJ \cdot min^{-1}$ for men and > 8 $kJ \cdot min^{-1}$ for women. Sitting time was also used to measure job related physical activity. This scale defined sedentary as > 6 $h \cdot d^{-1}$ sitting, moderate activity as 2-6 $h \cdot d^{-1}$ sitting, and high activity as < 2 $h \cdot d^{-1}$ sitting (11). Hours of sitting time were derived from imputed job titles rather than respondent self-report.

Complete lifetime occupational histories were available for 617 cases and 1,229 controls in the Iowa/Minnesota study. For these subjects lifetime cumulative and average levels of physical activity were also calculated. The midpoint values of the estimate of occupational EE (sedentary: 4 $kJ \cdot min^{-1}$; moderate: 10 $kJ \cdot min^{-1}$; highly active: 16 $kJ \cdot min^{-1}$) and sitting time (sedentary: 7 $h \cdot d^{-1}$; moderate: 4 $h \cdot d^{-1}$; highly active: 1 $h \cdot d^{-1}$) categories were used as weights for each job, multiplied by the duration of employment in that job, and summed over all jobs held by the subject. The cumulative occupational activity scores were divided by the total duration of employment to obtain the lifetime occupational average level of physical activity. The lifetime average levels were classified as sedentary, moderate, and heavy activity as described above for usual occupational levels.

Statistical analysis. The measure of association for estimating the risk of NHL and physical activity indices was the odds ratio (OR). OR were adjusted for age and state of residence. Further adjustments for vital status, solvent exposure, and hair dye use did not change the results and are not presented. Maximum likelihood estimates of the overall risk and corresponding 95% confidence intervals were calculated according to Gart's method (18). The lowest level of occupational physical activity (sedentary) served as the referent group. The test for trend in risk by level of occupational physical activity was calculated using the Mantel one tailed test (32).

RESULTS

There was no evidence of an association between NHL and physical activity measured either by EE or sitting time among men (Table 1). The OR associated with usual occupation moderate and high EE were 1.1 and 1.0, respectively. For sitting time, the OR were also 1.1 and 1.0 for moderate and high activity, respectively. Excluding farmers and farm managers, who have been found to have an increased risk of NHL (57), did not change the results appreciably. For EE, the OR were 0.9 and 1.0 for moderate and high levels, respectively, while for sitting time, the OR were 1.0 and 1.0 for moderate and high activity, respectively.

Subjects Physical Activity Index	Cases	Controls	Odds Ratio	95% Confidence Interval	Tread Test, *P*-Value
Men: All					
Energy					
Sedentary	333	1,047	1.0		
Moderate	573	1,535	1.1	0.9–1.2	Chi = 1.0
High	79	289	1.0	0.7–1.3	*P* = 0.460
Sitting time†					
Sedentary	195	611	1.0		
Moderate	546	1,516	1.1	0.9–1.4	Chi = 0.189
High	244	744	1.0	0.8–1.3	*P* = 0.425
Women: All					
Energy					
Sedentary	67	236	1.0		
Moderate	111	434	0.9	0.6–1.3	Chi = 0.477
High	2	4	1.7	0.2–11.5	*P* = 0.317
Sitting time†					
Sedentary	37	151	1.0		
Moderate	117	432	1.1	0.7–1.7	Chi = 0.498
High	26	91	1.2	0.7–2.3	*P* = 0.309
Men: Nonfarmers††					
Energy					
Sedentary	332	1,045	1.0		
Moderate	222	677	0.9	0.7–1.1	Chi = 0.602
High	79	289	1.0	0.7–1.3	*P* = 0.274
Sitting time†					
Sedentary	195	611	1.0		
Moderate	194	656	1.0	0.8–1.3	Chi = 0.312
High	244	744	1.0	0.8–1.3	*P* = 0.378
Women: Nonfarmers††					
Energy					
Sedentary	66	236	1.0		
Moderate	39	152	0.9	0.6–1.5	Chi = 0.101
High	2	4	1.7	0.2–11.7	*P* = 0.460
Sitting time†					
Sedentary	37	151	1.0		
Moderate	44	150	1.1	0.7–2.0	Chi = 0.666
High	26	91	1.2	0.7–2.3	*P* = 0.253

* Eight cases and 47 controls were excluded because 1) they never worked, 2) it was not possible to identify the usual occupation from the work history, 3) the usual occupation could not be classified as to physical activity, or 4) the age was unknown.
† Moderate activity = 2-6 h·d^{-1} spent sitting; high activity < 2 h·d^{-1} spent sitting

TABLE 1. Number of non-Hodgkin's lymphoma cases and controls and odds ratios for physical activity indices, adjusted by age and state of residence.*

Among women, slight elevations in risk of NHL were observed among the high energy level and high activity sitting category (Table 1). These increases, however, were not statistically significant and, for energy level, were based on small numbers of exposed subjects (2 cases and 4 controls). The trends were not significant. Among men and women there was no evidence of confounding or effect modification by vital status, hair dye use, or solvent exposure.

Table 2 presents OR for the lifetime cumulative and average physical activities among the men from the Iowa/Minnesota study, the only study which collected lifetime occupation histories. No significant increases or trends were observed. Nonsignificant ORs of 1.2 were observed for the moderate and high activity cumulative sitting time categories.

Physical Activity Index	Cases	Controls	Odds Ratio	95% Confidence Interval	Trend Test, *P* Value
Cumulative energy					
Sedentary	129	234	1.0		
Moderate	145	281	1.0	0.7–1.4	Chi = 0.231
High	343	714	1.0	0.7–1.4	*P* = 0.409
Cumulative sitting time†					
Sedentary	136	287	1.0		
Moderate	233	438	1.2	0.9–1.5	Chi = 0.876
High	248	504	1.2	0.9–1.6	*P* = 0.191
Average energy					
Sedentary	202	411	1.0		
Moderate	366	726	1.1	0.8–1.3	Chi = 0.596
High	49	92	1.1	0.7–1.7	*P* = 0.276
Average sitting time†					
Sedentary	67	130	1.0		
Moderate	424	841	1.0	0.7–1.4	Chi = 0.225
High	126	258	1.0	0.7–1.4	*P* = 0.411

† Moderate activity = 2-6 $h \cdot d^{-1}$ spent sitting; high activity < 2 $h \cdot d^{-1}$ spent sitting.

TABLE 2. Number of non-Hodgkin's lymphoma cases and controls and odds ratios for lifetime occupational cumulative and average level of physical activity, adjusted by age and state of residence, among men from Iowa and Minnesota.

DISCUSSION

This study evaluated the association between occupational physical activity and NHL in a combined data set of three case-control studies from eastern Nebraska, Kansas, Iowa, and

Minnesota. Among men, there was no association between NHL and EE or sitting time based on usual occupation or, among a subset of the data, on lifetime occupational histories. The 20% increase in NHL associated with moderate or active cumulative lifetime sitting time was not statistically significant. Among women, increased OR were observed for high levels of EE and sitting time, but the OR and trends were not significant. This general lack of an association is consistent with the nonsignificant trend in OR of 1.0 and 1.2 for NHL with moderate and low occupational physical activity, respectively, in comparison to high activity level, reported by Brownson et al. (6).

The measures of physical activity used in this study were based on occupation, which has some limitations. First, all persons within an occupation were assigned the same physical activity code regardless of inter-individual variation in the occupational physical activity (e.g., all farmers are assigned the same values for EE and sitting time despite heterogeneity in activities among farmers). Second, there was no information on nonoccupational activity (i.e., recreational and leisure time activity) which, among North Americans, is likely the more important contributor to daily physical activity and EE than occupational activity (44,52). Two of the three studies had information on usual occupation only, which provides less information than a complete occupational history. However, the results for Iowa/Minnesota, based on lifetime occupational histories, were consistent with the analyses based on usual occupation. The weaknesses in these occupation-based measures of physical activity would tend to bias risk estimates toward unity, obscuring any association that might be present.

Despite these limitations, these indices of EE and sitting time have been applied to the occupation held at the time of cancer diagnosis (or most recent occupation) and to lifetime occupational histories and were able to discriminate risk for colon cancer and other cancers in studies conducted in Turkey (11,50) and Shanghai (9). Similar indices developed by other researchers (6,7,17,19,39) have also been effective in demonstrating associations between occupational physical activity and cancers of the colorectum and breast (48). Therefore, if the study's limitations have obscured a true association between NHL and occupational physical activity, the association is probably weaker than those observed for colorectal and breast cancer.

Although few causal factors are known for NHL (e.g., human immunodeficiency virus (5), immunosuppression (12)), a variety of environmental factors have been associated with the risk of NHL, including HTLV (33), Epstein-Barr virus (33), pesticides (57), hair dye uses (59), and solvent exposure (35,38). It seems unlikely, however, that any of these factors have affected the results of this study. For example, although no data are available on HIV infection rates among the rural population of the Midwest in the early 1980s, the proportion infected was surely too low to confound this study's data. Similarly, HTLV-1 infection was probably rare. Infection with Epstein-Barr virus was more common, but its association with physical activity is not known. Pesticides were an important risk factor for NHL in this data set and should be evaluated as a potential confounding factor. Direct adjustment was not possible because all farmers were assigned the same physical activity measure on the basis of their occupation. Analyses that excluded all farmers and farm managers, however, yielded results similar to those for the total population. Hair dye use and solvent exposure were evaluated directly and had no effect on the results.

Although this study showed no association between occupational physical activity and NHL, laboratory evidence suggests that exercise affects immune regulation, which in turn may contribute to the risk of NHL. Lymphocyte proliferation is normally tightly regulated by cytokines and growth factors, so factors which influence stimulatory signals to lymphocytes may contribute to immune dysregulation and lymphoma development (21). The impact of exercise on cytokine responses, including interleukins IL-1, IL-2, IL-6, tumor necrosis factor (TNF), and interferon, has been documented experimentally (2,20). For example, IL-6 concentration in plasma increases in response to exercise (37,40-42,46) and soluble IL-2 receptor levels increase, suggestive of increased T-cell activation with heavy exercise (3,29). Moreover, since many cytokines play a role in regulation of cellular adhesion molecules, heavy exercise is also accompanied by alterations in the expression and function of cell adhesion molecules that play a role in lymphocyte trafficking (16,25). Recent evidence shows that IL-6 and IL-10 are produced by NHL cells and may act as cooperative growth factors to enhance NHL cell proliferation (51).

In summary, we found no association between occupational physical activity and risk of NHL. The measures of physical activity used in this study had limitations, although other studies using similar methodologies have reported increased risks of colorectal and breast cancers with increasing sedentariness. Therefore, the true association for occupational physical activity and NHL, if any, is likely to be weaker than that for colorectal or breast cancer. There are reasons, however, for further research on this possible association. First, this study's data were limited to occupational activity with no information on nonoccupational activity, which is more important for most adults in the U.S. Second, there is laboratory evidence linking physical activity and immune function, which is important in the etiology of NHL. Further studies are needed 1) to determine whether nonoccupational physical activity modifies risk of NHL; 2) to evaluate the effects of the timing of the physical activity during one's lifetime and relative to cancer diagnosis; and 3) to evaluate possible interaction between physical activity and known risk factors, such as pesticides, HIV, and EBV.

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